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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/245,198	02/05/99	BROWNING J	A003

HM12/0411

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EXAMINER	
KERR, J	
ART UNIT	PAPER NUMBER
1633	15

DATE MAILED: 04/11/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/245,198	BROWNING ET AL.	
	Examiner	Art Unit	
	Janet Kerr	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 January 1935* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *11-25,27 and 32-35* is/are withdrawn from consideration.

5)☒ Claim(s) *2 and 3* is/are allowed.

6)☒ Claim(s) *1,4-10,26 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☒ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

Response to Amendment

Applicants' amendment, filed 1/12/01, has been entered in part. The request amending page 37, line 16 of the specification has not been entered as there is no mechanism for determining spaces on a page. It is suggested that applicants submit an amended Table. It is also noted that applicants have submitted a paper copy of the sequence listing but have not directed its entry into the specification.

This application contains claims 11-25, 27, and 32-35, drawn to an invention nonelected with traverse in Paper No. 8. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Claims 1-35 remain pending.

Claims 1-10, 26, and 28-31 are being examined on the merits.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because: the declaration claims foreign priority benefits under 35 U.S.C. 119(a)-(d) or 365(a)-(b). However, PCT/US97/13945 is not a foreign application.

1) The declaration indicates that the instant application claims foreign priority benefits under 35 USC 119(a)-(d) or 365(a)-(b) wherein the prior foreign application is PCT/US97/13945. However, PCT/US97/13945 is not a foreign application.

2) The declaration further indicates that the instant application claims benefit of priority under 35 USC 119(e) with respect to provisional applications 60/023,541, filed August 7, 199, 60/028,515,

filed October 18, 1996, and 60/040,820, filed March 18, 1997. The instant application is not entitled to benefit of priority to the provisional application as the provisional applications were filed more than one year prior to the filing of the instant application. It appears, however, that the PCT application claims benefit of priority to the provisional applications. If applicants intended that the instant application is a continuation of the PCT application, and the PCT application claims benefit of priority to the provisional application, then a new declaration should be submitted to reflect the appropriate benefit of priority claims.

Specification

The disclosure is objected to because of the following informalities: on page 1, first paragraph, the continuity data is listed incorrectly as discussed above. Appropriate correction is required.

The amendment filed 1/12/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the added material at page 34, line 9, and at page 35, lines 9 and 13 does not appear to be supported by the original disclosure. Applicant is required to cancel the new matter in the reply to this Office action or to specifically point out pages and line numbers in the specification which support the added material.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirement of 37 CFR 1.821(d) as reference must be made to each of the sequences disclosed in Figures 1 and 2, either in the figure or in the text of the description of the figure, by use of a sequence identifier, preceded by "SEQ ID NO:".

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 10, and 26 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to polynucleotides comprising SEQ ID NOS: 1 and 3 and polynucleotides encoding polypeptides comprising the amino acid sequences set forth in SEQ ID NOS: 2 and 4, and equivalents of SEQ ID NOS: 1 and 3, vectors and hosts comprising the polynucleotides, polynucleotides hybridizable to portions of SEQ ID NOS: 1 and 3, polynucleotides comprising conservative substitutions, deletions, or alterations which do not abolish the biological activity of TRELL, antisense nucleic acids comprising a nucleic acid sequence hybridizing under stringent conditions to at least a portion of SEQ ID NO: 1 or 3 effective to inhibit expression of TRELL.

While the specification adequately describes polynucleotides encoding TRELL polypeptides, wherein the polynucleotides consist of the nucleic acid sequences set forth in SEQ ID NOS: 1 and 3, and polynucleotides encoding TRELL polypeptides, wherein the polypeptides consist of the amino acid sequences set forth in SEQ ID NOS: 2 and 4, the specification fails to provide any sequence data for polynucleotide equivalents, polynucleotides hybridizable to the nucleic acid sequences set forth in SEQ ID NOS: 1 or 3, polynucleotides comprising deletions, substitutions, or alterations, polynucleotides comprising the nucleic acid sequences set forth in SEQ ID NOS: 1 and 3, i.e., TRELL genes, or antisense nucleic acids. As there is no disclosure of

any polynucleotides other than those set forth in the specification as SEQ ID NOS: 1 and 3, the specification does not provide an adequate written description for the polynucleotides instantly contemplated.

The disclosure does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for any non-disclosed polynucleotide, including promoter and intronic sequences, hybridizable sequences, antisense sequences, sequences with alterations, deletions, mutations, etc. While applicants were obviously in possession of the nucleic acid sequences as set forth in the disclosed SEQ ID NOS: 1 and 3, the specification provides no information regarding the broadly claimed nucleic acid constructs. The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of polynucleotides besides the disclosed SEQ ID NOS., at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genera.

The instant application does not provide a written description that would allow one of skill in the art to immediately envisage the specific structure for operative fragments or non-murine homologues or operative derivatives. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

As there is no disclosure of the polynucleotides, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

The limited information provided in the specification is not deemed sufficient to reasonably convey to one skilled in the art that Applicants were in possession of the broadly claimed polynucleotides at the time the application was filed. Thus it is concluded that the written description provision of 35 U.S.C. §112, first paragraph, is not satisfied for the claimed polynucleotides. Applicants are reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Newly amended claim 4 recites the limitation of "said DNA sequence encoding a polypeptide that is at least 30% homologous with the receptor binding domain of TRELL". It is noted that the specification only discloses that "the invention relates to sequences that have at least 50% homology with the DNA encoding the C terminal receptor binding domain of TRELL" (see page 7, lines 15-17 of the instant application). However, there is no written description in the specification with respect polynucleotides encoding polypeptides that are at least 30% homologous with the receptor binding domain of TRELL, there are no DNA sequences identified by SEQ ID NO. which correspond to the claimed polynucleotides, nor is there recitation of such polynucleotides in the claims as originally filed. In addition, with regard to the recitation of "stringent conditions", while the specification details specific hybridization conditions on pages 30 and 34 of the instant application, there is no disclosure of hybridization conditions which are defined as "stringent conditions". Applicants are required to cancel the claim or amend the claim such that the claimed invention is supported by the disclosure in the instant application.

This is a new matter rejection.

Applicant's arguments filed 1/12/01 have been fully considered but they are not persuasive.

It is argued, on pages 8-9 of applicants' Response, that the present application discloses full open reading frames from mouse and human nucleic acid sequences that encode TRELL

polypeptides and that one of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 1 or SEQ ID NO: 3 because these sequences can be readily embedded in known vectors as understood in the art and as disclosed on page 12, line 3 to page 13, line 10 of the instant application. It is argued that one of skill in the art would recognize from the disclosure that applicants were in possession of the genus of DNAs that comprise SEQ ID NOS: 1 and 3 as claimed in the present invention.

These arguments are not persuasive for the following reasons. With regard to claims directed to polynucleotides comprising nucleic acid sequences set forth in SEQ ID NOS: 1 or 3, the claims encompass genes. As the specification does not set forth any polynucleotides comprising promoter and intronic sequences, the specification fails to provide adequate written description of polynucleotides comprising the nucleic acid sequences set forth in SEQ ID NOS: 1 or 3. With regard to polynucleotide equivalents, the specification does not provide a definition of a polynucleotide equivalent, i.e., the specification defines a polynucleotide equivalent in terms of a polypeptide equivalent (see page 11 of the instant application). Given the lack of a definition of a polynucleotide equivalent, one of skill in the art could not envision the structural features of the claimed polynucleotide equivalents. With regard to claims directed to polynucleotide variants, i.e., polynucleotides comprising deletions, alterations, or substitutions, wherein the deletions, alterations, or substitutions do not abolish the biological activity of TRELL, the specification fails to provide any such sequences. Moreover, as it is not readily apparent from the specification what is meant by "biological activity" (the specification defines "biologically active" as having an *in vivo* or *in vitro* activity which may be performed directly or indirectly, see page 10, lines 23-24 of the instant application), and in view of the teachings of Darnay *et al.* that the biological activity of TRELL appears to be cell-type dependent (see page 8 of the previous Office action), one of skill in the art could not envision the structures of polynucleotides comprising deletions, alterations or substitutions wherein the deletions, alterations or substitutions do not abolish biological activity of TRELL. With regard to antisense nucleic acids, the specification does not provide any polynucleotides which hybridize to and inhibit expression of TRELL. With regard to

DNA sequences that hybridize under stringent conditions to at least a fragment of SEQ ID NOS: 1 or 3, the fragment comprising at least 20 consecutive bases, said DNA sequence encoding a polypeptide that is at least 30% homologous with the receptor binding domain of TRELL, the specification does not provide any such sequences. As stated above, adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. Thus, for the reasons of record and the reasons set forth above, the rejection is maintained.

Claims 1, 4-8, 10, 26, and 28-31 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for polynucleotides set forth in SEQ ID NOS: 1 and 3, said polynucleotides encoding TRELL polypeptides set forth in SEQ ID NOS: 2 and 4, and vectors and host cells comprising the polynucleotides, methods of making the polypeptides having the amino acid sequences set forth in SEQ ID NOS: 2 and 4, does not reasonably provide enablement for equivalents of SEQ ID NOS: 1 and 3, a recombinant DNA molecule comprising a DNA sequence encoding TRELL operatively linked to an expression control sequence, DNA sequences which hybridize under stringent conditions to at least a fragment of SEQ ID NO: 1 or SEQ ID NO: 3, DNA sequences with conservative substitutions, alterations, or deletions, antisense nucleic acids against TRELL, a method of expressing a gene in a mammalian cell or a method of treating a disorder related to TRELL. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While the specification is enabling for polynucleotides set forth in SEQ ID NOS: 1 and 3, said polynucleotides encoding TRELL polypeptides set forth in SEQ ID NOS: 2 and 4, and vectors and host cells comprising the polynucleotides, methods of making the polypeptides having the amino acid sequences set forth in SEQ ID NOS: 2 and 4, the specification is not enabling for TRELL genes, polynucleotide variants of SEQ ID NOS: 1 and 3, antisense constructs,

polynucleotides which are hybridizable to fragments of SEQ ID NOS: 1 and 3, a method of expressing TRELL in a mammal, or a method of treating a disorder comprising administering a TRELL polynucleotide for the reasons set forth on pages 7-15 of the Office action of 7/14/00.

Applicant's arguments filed 1/12/01 have been fully considered but they are not persuasive.

It is argued, on page 8 of applicants' Response, that the specification (1) discloses TRELL nucleic acids and equivalents, the production of expression vectors, and transformation of appropriate hosts to produce TRELL (pages 11-14 of the instant application), (2) discloses the use of the nucleic acids in gene therapy and antisense therapy (pages 13-14), and (3) provides approaches to constructing oligomers useful in antisense therapy (page 14, lines 7-10 of the instant application). Applicants have provided references attached as Exhibit A which provide reviews the art of antisense technology.

These arguments are not persuasive for the following reasons.

With regard to substantially pure nucleic acids comprising sequences set forth in SEQ ID NOS: 1 or 3, the specification clearly encompasses genomic DNA in the definition of substantially pure nucleic acids (see page 10, lines 17-18 of the instant application). As the specification has not provided any exemplification of genomic sequences, and has not provided guidance with respect to how to use such genomic sequences, the specification is non-enabling for the claimed polynucleotides encompassing TRELL genomic sequences.

With regard to TRELL nucleic acids equivalents, the specification does not provide a definition of a nucleic acid equivalent. On page 11, lines 5-8, the specification states that "The term nucleic acid as used herein can include fragments and equivalents, such as, for example, sequences encoding functionally equivalent peptides. Equivalent nucleotide sequences may include sequences that differ by one or more nucleotide substitutions, additions or deletions, such as allelic variants, mutations, etc...". However, the specification does not disclose any polynucleotides comprising substitutions, additions or deletions, allelic variants, mutations, etc. Moreover, the specification does not disclose any amino acid sequences of functionally equivalent

peptides. One of skill in the art would not know how to make "equivalent polynucleotides" which encode functionally equivalent peptides without undue experimentation.

With regard to polynucleotides which hybridize to fragments of SEQ ID NOS: 1 or 3 and which encode a polypeptide that is at least 30% homologous with the receptor binding domain of TRELL, the specification does not disclose any such polynucleotides or guidance as to how to use these polynucleotides. Moreover, while the specification details specific hybridization conditions on pages 30 and 34 of the instant application, there is no disclosure of hybridization conditions which are defined as "stringent conditions". In addition, given the known structural and functional diversity of the family members of TNF (discussed in the previous Office action), one of skill in the art would not know what, if any, functional activity a polypeptide encoded by the claimed polynucleotide would have, and therefore would not know how to use such a polynucleotide.

With regard to making and using antisense constructs to inhibit TRELL expression, while the general technology of generating antisense constructs is established, as evidenced by the references submitted as Exhibit A, generating a specific antisense construct which inhibits the expression of a particular gene is an unpredictable art as set forth in the teachings of Branch and Agrawal (see pages 12-15 of the previous Office action). The specification does not provide sufficient written description of the construct, sufficient guidance in making the construct, or any working example of an antisense nucleic acid which is capable of inhibiting expression of TRELL. Given the state of the art of antisense technology, the lack of guidance in the specification, and the lack of a working example of an antisense construct which inhibits TRELL expression, it would require undue experimentation to make or use the claimed antisense construct.

With respect to claims encompassing gene therapy, the specification only generally discloses that the instant DNA sequences can be used to express TRELL under abnormal conditions. The sequences could be expressed in tumor cells under the direction of promoters appropriate for such applications and such expression could enhance anti-tumor immune responses or directly affect the survival of the tumor. In addition, the sequences can be used to

affect the survival of an organ graft by altering the local immune response (see page 13 of the instant application). However, the specification does not disclose abnormal conditions which can be treated by expressing a polynucleotide encoding TRELL, nor does the specification disclose the types of tumors in a patient which could be treated by expressing a polynucleotide encoding TRELL. In addition, the specification does not disclose any alterations in the local immune response as a function of the expression of a polynucleotide encoding TRELL. The specification does not disclose appropriate promoters to use, appropriate target sites for delivery of the polynucleotide, appropriate expression vectors required in the delivery of the polynucleotide, or the level of expression of the polynucleotide such that an anti-tumor response or an alteration in the local immune response is achieved. It is further noted that the specification discloses that only 1 cell line of 11 cell lines tested *in vitro* displayed any response to a TRELL peptide, and this response required the presence of interferon-gamma (see Table II on page 37 of the instant application). Clearly, the showing in the specification is not commensurate in scope with applicants' arguments that *in vitro* testing of the polypeptide is sufficient evidence of an enabling disclosure for gene therapy. Thus, as stated in the previous Office action, the specification is non-enabling for using the nucleic acids in gene therapy protocols as the specification does not disclose methods by which the skilled artisan could predictably and reproducibly introduce and express TRELL polynucleotides in a mammal, nor does the specification provide sufficient guidance for practicing the claimed method of treating a disorder related to TRELL in a mammal. Given the lack of guidance in the specification as to how to practice the claimed methods, and the unpredictability in the art of delivering and expressing polynucleotides in a mammal as discussed in the previous Office action, one of skill in the art could not practice the claimed invention without undue experimentation.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 10 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered vague and indefinite by the term "equivalent" as it is unclear if by equivalent applicants intended, for example, the same size, the same structure, and/or the same function. The metes and bounds of the claim are unclear.

Claim 10 is rendered vague and indefinite by the phrase "substantially purifying" as it is unclear from the claim and the specification what steps are required in a substantial purification protocol. If applicants intended that the TRELL is isolated from the transformed host and substantially purified, then applicants should amend the claim to read "...host of claim 8, and isolating TRELL from the transformed host to obtain substantially purified TRELL".

Applicant's arguments with respect to claims 1 and 10 have been considered but are moot in view of the new ground(s) of rejection.

Claims 1, 4-10, 26, and 28-31 remain rejected for the reasons of record and the reasons discussed above.

Claims 2 and 3, as amended, are allowable.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet M. Kerr whose telephone number is (703) 305-4055. Should the examiner be unavailable, inquiries should be directed to Deborah Clark, Supervisory Primary Examiner of Art Unit 1633, at (703) 305-4051. Any administrative or procedural questions should be directed to Kimberly Davis, Patent Analyst, at (703) 305-3015. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 305-7401.

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